SODIUM BOROHYDRIDE MEDIATED BENZYLATION OF 1,3-DIMETHYLBARBITURIC ACID

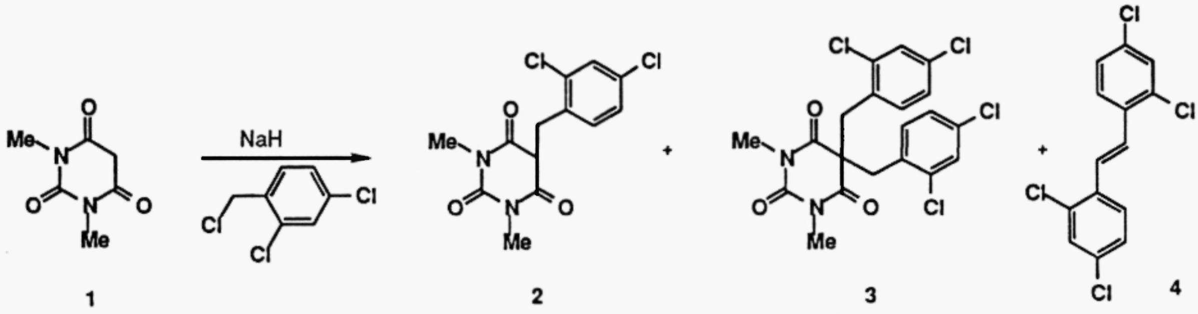
Lucjan Strekowski* and Mohamed A. Ismail[‡]
Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, USA

Hanafi H. Zoorob
Faculty of Science, Al-Mansoura University, Al-Mansoura, Egypt

Abstract: The reaction of 1,3-dimethylbarbituric acid with one or two equiv of a benzyl chloride in the presence of one equiv of $NaBH_4$ in DMF furnishes selectively the respective 5-benzyl or 5,5-dibenzyl derivative in high yield.

1,3-Dialkylbarbituric acids substituted at C5 can be obtained by ring construction or derivatization of the parent compounds (1,2). The latter reaction is often inefficient. In particular, it has been reported that treatment of 1,3-dimethylbarbituric acid (1) with benzyl chloride in the presence of sodium hydroxide gives the 5-benzyl derivative in a 33% yield (3,4).

We found that the efficiency of the benzylation can be substantially improved by conducting the reaction in DMF with NaH as a base. The following procedure is representative. A mixture of 1 (156 mg, 1 mmol) and NaH (24 mg, 1 mmol) in anhydrous DMF (5 mL) was stirred under a nitrogen atmosphere at 23 °C for 20 min and then the resultant solution of a sodium derivative of 1 was allowed to react with 2,4-dichlorobenzyl chloride (196 mg, 1 mmol) at 60 °C for 8 h. Concentration on a rotary evaporator followed by treatment of the residue with ice water and acidification with hydrochloric acid gave a precipitate of **2** (eq. 1). After crystallization from $EtOH/CHCl_3$ (1:1) the yield of **2** was 73% (5). A GC-MS analysis revealed that the balance of material consisted of the starting material 1, its dibenzyl derivative 3, and a stilbene **4**. On the other hand, an attempted one-pot preparation of 3 from **1** (1 equiv), NaH (2 equiv), and the benzyl chloride (2 equiv) gave stilbene **4** as the major product (70%) accompanied by small amounts of **2** and **3** (about 10% each). The efficient formation of stilbenes by the reaction of the corresponding benzyl halides and NaH has been noted previously (6).



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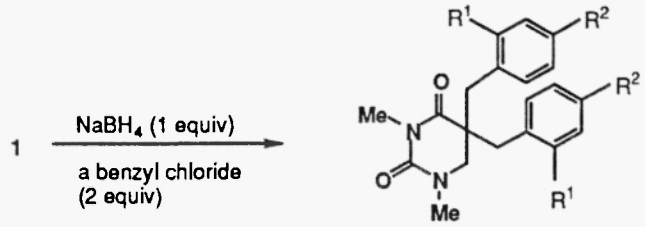
[‡] A CHANNEL student from Al-Mansoura University.

It was reasoned that the preparation of the disubstituted derivative **3** could be made practical by conducting the reaction in DMF in the presence of a base that does not promote the formation of a stilbene from the benzyl substrate. Accordingly, many reactions of **1** with 2,4-dichlorobenzyl chloride in the presence of amines of various steric hindrance and basicity and in the presence of inorganic bases including LiOH, NaOH, KOH, and K_2CO_3, were attempted. To our surprise, the best results were obtained with sodium borohydride. Not only was the yield of the monosubstituted derivative **2** improved from 73% to 78% by substituting $NaBH_4$ for NaH in the procedure given above but also the dibenzyl product **3** could be obtained in an 83% yield (eq 2). The iatter reaction was conducted by using **1** (1 mmol), 2,4-dichlorobenzyl chloride (2 mmol), and $NaBH_4$ (1 mmol) under otherwise identical conditions. Following the workup described above, the product **3** was crystallized from ethanol. Additional dibenzyl-substituted barbituric acids **5-8** were obtained in a similar manner (eq 2). The structure of **3** was established by x-ray diffraction crystallographic analysis, and all products **3, 5-8** were characterized by ^1H and ^{13}C NMR (5). The formation of a stilbene was not observed in all these reactions conducted in the presence of $NaBH_4$.



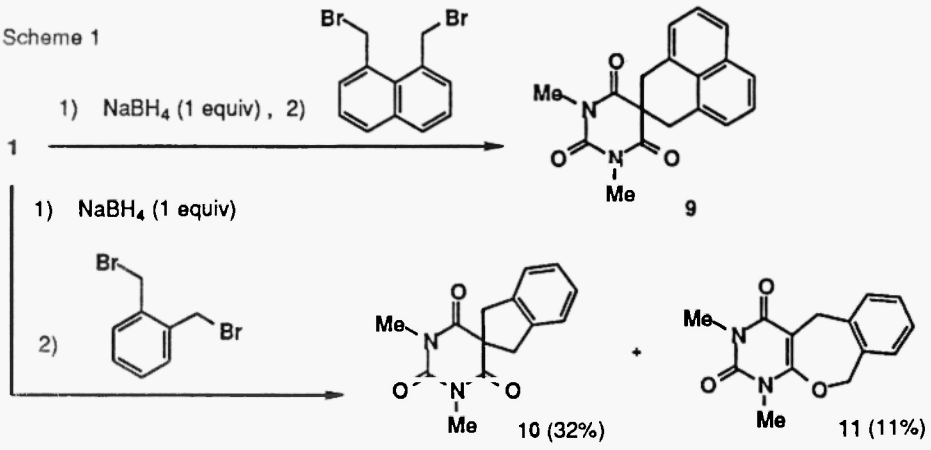
No	R^1	R^2	yield %
3	Cl	Cl	83
5	H	Cl	91
6	H	Br	74
7	H	F	84
8	H	H	82

(2)

3, 5-8

The results described above clearly indicate that the use of $NaBH_4$ over other bases including NaH is strongly advantageous in the synthesis of 5,5-dibenzyl-substituted barbituric acids. As an extension of this work the synthesis of two spiro derivatives is given in Scheme 1. Thus, the treatment of **1** with $NaBH_4$ (1 equiv) followed by addition of 1,8-bis(bromomethyl)naphthalene (1 equiv) by using the general procedure gave the spiro compound **9**. This product was

Scheme 1



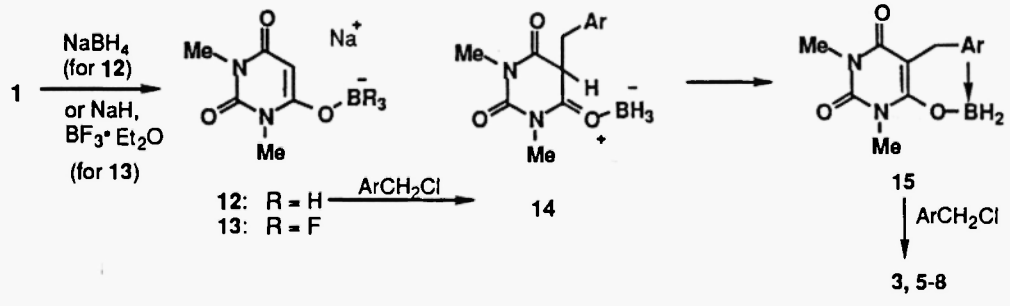
obtained in a 63% yield after simple crystallization from ethanol. The given structure of **9** is fully consistent with the ^1H and ^{13}C NMR data and was confirmed by x-ray diffraction crystallographic analysis. On the other hand, a similar reaction of **1** with 1,2-bis(bromomethyl)benzene gave a mixture of the expected spiro compound **10** and a benzoxepin derivative **11**. The separation of these products required chromatography (silica gel, pentanes/AcOEt, 4:1). Product **10** was eluted in the first fractions. After crystallization from ethanol the yields of **10** and **11** were 32% and 11%, respectively. It should be noted that the analogous reactions conducted in the presence of NaH instead of $NaBH_4$ gave complicated mixtures with **10** and **11** as the minor products. The structures of the isomeric compounds **10** and **11** were assigned unambiguously by analysis of the NMR data. Thus, the symmetrical spiro compound **10** gave a four-proton singlet for the two methylene groups in the ^1H NMR spectrum (δ 3.46 in DMSO-d_6) and the expected eight signals in the ^{13}C NMR spectrum. By contrast, the chemical shifts for protons of the two methylene groups in **11** are distinctly different (δ 3.98 and 5.55 in DMSO-d_6), and the ^{13}C NMR spectrum consists of fourteen signals corresponding to the fourteen nonequivalent carbons in the molecule.

In a brief study of the scope and limitations of this novel reaction the enolate generated in DMF from **1** in the presence of $NaBH_4$, NaH or other bases mentioned above (1 or 2 equiv) was allowed to react with ethyl iodide (1 or 2 equiv). In all cases studied the desired monoethyl derivative was obtained in a low yield and always in a mixture with a diethyl-substituted 1,3-dimethylbarbituric acid. In the experiments designed toward the preparation of the latter product the use of either $NaBH_4$ or NaH resulted in a yield of about 50%. In summary, it can be concluded that the $NaBH_4$-mediated alkylation of **1** is of practical value for the selective introduction of either one or two benzyl groups at position 5 of the substrate (7).

In order to understand the peculiar role $NaBH_4$ plays in the benzylation reactions, experiments with varying amounts of the reagents were conducted. As already indicated, it was found that the optimized ratio of **1** to $NaBH_4$ is 1:1 for both the mono- and dibenzylation reactions. In another experiment the substrate **1** in DMF was treated with NaH (1 equiv) followed by addition of trifluoroboron etherate (1 equiv) to the resultant enolate of **1** and then 2,4-dichlorobenzyl chloride (1 equiv). This attempted reaction did not produce the expected product **2**, and the starting material **1** was isolated in a virtually quantitative yield.

These results can be explained in terms of the mechanistic pathway suggested in Scheme 2. It is reasonable to assume that the initial reaction of **1** with $NaBH_4$ generates a boron complex **12** which then undergoes a nucleophilic substitution reaction with a benzyl chloride (S_N2 and/or S_N1) to generate another complex **14**. This intermediate compound is a direct precursor to a monobenzylated product, such as **2**. In full agreement with this proposed mechanism the analogous complex **13** containing a strongly electron-withdrawing trifluoroboryl substituent is not nucieophilic

Scheme 2



enough to undergo a substitution reaction with a benzyl reagent, as observed. On the other hand, the complex **14** may undergo an intramolecular enolization to give **15** which is then benzylated. A driving force for this enolization may be complexation of the electron-deficient boron atom by the π-electron-rich phenyl group in **15**. For the stereoelectronic reason the phenyl group in the complex **15** must be approximately perpendicular to the pyrimidine moiety. This feature would hinder a reaction of **15** with a benzyl reagent, thereby giving rise to high selectivities of the mono- and dibenzylation reactions, also as observed.

References and Notes

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(5) All new compounds gave satisfactory results of elemental analysis (C ± 0.3, H ± 0.2, N ± 0.2%). Unless otherwise stated the ^{13}C NMR spectra reported below (100 MHz) were recorded in $CDCl_3$. **2**: mp 162-162.5 °C; ^{13}C NMR δ 167.5, 151.3, 134.9, 134.1, 132.7, 132.3, 129.5, 127.2, 49.6, 33.7, 28.7
3: mp 164-165 °C; ^{13}C NMR δ 169.6, 150.1, 135.5, 134.1, 131.5, 131.0, 129.8, 127.1, 57.3, 40.6, 28.8
4: mp 159-160 °C [reported mp 158-159.5 °C, ref. 6; reported mp 161-161.5 °C, D. Hoeg and D. Lusk, J. Organomet. Chem. *5*, 1 (1966)]; ^{13}C NMR δ 134.2, 134.1, 133.5, 129.6, 127.6, 127.4, 126.6
5: mp 212-213 °C; ^{13}C NMR δ 170.4, 149.6, 133.7, 133.2, 130.5, 128.7, 60.6, 44.3, 28.1
6: mp 211-212 °C; ^{13}C NMR δ 170.4, 149.6, 133.8, 131.7, 130.9, 121.9, 60.5, 44.4, 28.1
7: mp 169-170 °C; ^{13}C NMR δ 170.6, 163.8, 160.5, 149.7, 130.9, 130.8, 130.6, 115.6, 115.3, 61.0, 44.1, 28.0 (these data include coupling with F)
8: mp 129-130 °C (reported mp 129.5-130 °C, refs. 3 and 4)
9: mp 125-127 °C; ^{13}C NMR δ 170.7, 151.3, 132.7, 130.6, 128.1, 126.8, 125.7, 124.2, 50.3, 37.6, 28.9
10: mp 138-139 °C; ^{13}C NMR (DMSO-d_6) δ 172.3, 151.5, 139.9, 126.7, 123.8, 55.3, 43.5, 28.5
11: mp 240-242 °C; ^{13}C NMR (DMSO-d6) δ 162.6, 157.2, 149.9, 141.0, 134.1, 129.6, 128.9, 128.1, 127.0, 88.1, 71.6, 28.8, 28.1, 27.0

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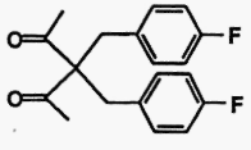
(7) The reaction of pentane-2,4-dione with $NaBH_4$ (1 equiv) and 4-fluorobenzyl chloride (2 equiv) by using the general procedure furnished product (i) in a 77% yield. In a similar way, compound (ii) was obtained in a 67% yield starting with indane-1,3-dione. Although these results demonstrate the generality of our method, much more efficient benzylation reactions of β-diketones are known.



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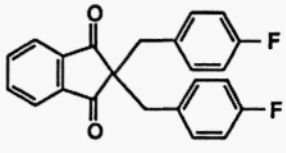

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